Schizophrenia Bulletin vol. 32 no. 3 pp. 507–524, 2006
doi:10.1093/schbul/sbj078
Advance Access publication on May 17, 2006

Neuropsychological Functioning in Adolescents and Young Adults at Genetic Risk for Schizophrenia and Affective Psychoses: Results from the Harvard and Hillside Adolescent High Risk Studies

Larry J. Seidman[1–4], Anthony J. Giuliano[2], Christopher W. Smith[5], William S. Stone[2,4], Stephen J. Glatt[6,7], Eric Meyer[2], Stephen V. Faraone[8], Ming T. Tsuang[2–4,6], and Barbara Cornblatt[5]

[2]Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center Division of Public Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA; [3]Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital, Boston; [4]Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA; [5]Department of Psychiatry Research, Zucker Hillside Hospital, North Shore–Long Island Jewish Health System (NSLIJHS), Glen Oaks, NY; [6] Department of Psychiatry, Center for Behavior Genomics, University of California, San Diego, La Jolla, CA; [7]Veterans Medical Research Foundation, San Diego, CA; [8]Medical Genetics Research Center and Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY

Siblings and offspring of persons with schizophrenia carry elevated genetic risk for the illness and manifest attentional and memory impairments. Because less is known about other neuropsychological functions and their specificity in adolescents, we conducted a genetic high-risk (HR) study of schizophrenia (HR-SCZ) and affective psychosis (HR-AFF). Participants (ages 12–25) were from the Harvard Adolescent High-Risk and Hillside Family studies, including 73 HR-SCZ, 18 HR-AFF, and 84 community controls (CCs) recruited in metropolitan Boston and New York. Groups were compared on overall neurocognitive functioning, 6 domains, and 13 test scores, controlling for age, parental education, and correlated data within families. The HR-SCZ group was significantly impaired overall, while the HR-AFF group demonstrated a trend toward overall impairment. HR-SCZ subjects showed significantly lower Verbal Ability ($d = .73$) and Executive Functioning/Working Memory ($d = .47$) than CCs. HR-AFF subjects showed reduced Verbal Ability ($d = .64$) compared to CCs. Excluding 12 CCs with a parental history of depression (without psychosis) led to larger differences between HR and CC groups across domains. Moreover, HR-SCZ and CC group differences in Verbal Memory ($d = .39$) and Visual-Spatial ($d = .34$) became statistically significant. There were no significant differences between HR-SCZ and HR-AFF groups. Data support a modest neuropsychological deficit in persons at genetic HR for psychosis, with a broader range of deficits in HR-SCZ. Future work should assess the relationship of neurocognition to adaptive functioning and possible onset of psychosis in HR samples. Ascertainment criteria for controls may markedly influence results and interpretation of group differences.

Key words: schizophrenia/affective psychoses/genetics/neurocognition/intelligence

Introduction

Schizophrenia is a neurobiologically based disorder with a multifactorial etiology that includes both genetic and environmental influences.[1] Family, twin, and adoption studies provide compelling evidence for a spectrum of disorders in which schizophrenia is the most severe expression of an illness that includes nonpsychotic features in addition to symptoms of psychosis.[2,3] One of these features, neuropsychological dysfunction, has come to be regarded as a core component of the disorder[4–7]; notably, cognitive deficits were considered central to the illness when it was first described by Kraepelin[8] and Bleuler.[9] Among individuals with schizophrenia, neuropsychological deficits contribute to overall levels of dysfunction and significantly influence functional outcome.[4,10] Moreover, the relatively modest improvement in neurocognition after either typical[11] or atypical[12,13] antipsychotic treatment, despite reasonably effective reduction in positive symptoms (eg, hallucinations), suggests the relative independence of neurocognition from positive symptoms in people with schizophrenia. Thus, understanding the nature of neurocognition in schizophrenia is relevant to providing clues to the etiology and pathophysiology of the disorder and improving treatment.

The view that schizophrenia is a neurodevelopmental disorder[14,15] originating at conception or during pregnancy is increasingly well accepted. The presence of neurodevelopmental features does not rule out the possibility

[1]To whom correspondence should be addressed; e-mail: lseidman@bidmc.harvard.edu.

that deterioration and even degeneration also take place during the premorbid period, around the first psychotic episode, or later in life. In fact, some have proposed that schizophrenia involves both neurodevelopmental and neurodegenerative processes.[16] Such a model accords well with a nascent literature focusing on the "prodromal" period—that is, the phase of descent into psychosis marked by increasing impairments in cognition and adaptive functioning as the illness develops.[17–19] Such conceptualizations posit the notion that some neurocognitive deficits precede the onset of frank psychosis.

The assessment of neurocognitive deficit as a risk or vulnerability factor that can be observed independent of psychosis in persons with schizophrenia or their relatives has been studied using at least 6 different populations: biological relatives at genetic high risk (HR) including twins, clinical HR ("prodromal") cases, spectrum cases such as those having schizotypal personality disorder, psychometric "at-risk" subjects identified using questionnaires with empirical cutoff scores, prospective population birth cohorts, and follow-back studies of people with schizophrenia. While all of these approaches have made important contributions to identifying and understanding the neurocognitive risk factors for schizophrenia, herein we focus on genetic HR approaches, as they form the basis for the data presented in this article.

The genetic HR approach is based on the fact that genetic influences are among the best-established risk factors for schizophrenia, with heritability estimated at approximately 60–90%.[20] Nonpsychotic first-degree relatives of people with schizophrenia (either offspring or siblings), who on average share 50% of genes with their ill relatives but are free of confounds associated with psychosis (eg, they are typically unmedicated), provide a unique opportunity to study genetic risk for the pathophysiology of schizophrenia over the life course. Assessment of relatives who have passed through the age of peak risk for schizophrenia (> age 30) allows identification of components of the syndrome that are independent of psychosis. The study of younger HR relatives (< age 30) provides an opportunity to identify the neurobiological differences present prior to typical onset of schizophrenia in a subset of relatives.

A large number of neuropsychological studies of schizophrenia families have targeted older adults (ages 30–60) who have passed through the peak period of risk for schizophrenia without developing psychosis, and these data have been well reviewed elsewhere.[21–26] Meta-analyses document that adult relatives manifest deficits on tasks of sustained attention, declarative and working memory, perceptual-motor speed, verbal fluency, and some executive functions,[25,26] supporting other qualitative reviews that have emphasized impaired attentional processing.[5,27] These data are consistent with a model that suggests a common difficulty in high-load executive control processing. Related studies show that deficits in executive control processes and memory dysfunctions are stable over time in adulthood[28] and are associated with degree of genetic loading,[29] thus index genetic liability.

There is also a substantial literature on genetic HR studies of young relatives, usually offspring, using cognitive measures. There are at least 20 genetic HR studies, most of them summarized by Niemi et al. (2003)[30], with the exception of the 4 most recently conducted studies that are just beginning to yield data: the Pittsburgh,[31] Harvard,[32,33] and Hillside Hospital studies[34] of teenagers and young adults and the Colorado study of children ages 6–15.[35] The previous studies have yielded substantial neurocognitive data that are summarized in Table 1. These studies have used numerous tests, are based on different sample sizes, tested people at different ages ranging from age 4 to 29, and employed different ascertainment approaches to identify HR and control samples, thus limiting firm conclusions. However, there is reasonably strong support for impairments in the following neurocognitive functions in relation to genetic risk for schizophrenia: attention and working memory (including sustained attention and vigilance, perceptual-motor speed, short-term and working memory), concept formation and abstract reasoning, verbal-linguistic ability (including receptive language), general intelligence, and declarative memory, especially verbal memory. These deficits are similar to those observed in older relatives ascertained mainly from family studies and are milder than those observed in persons with schizophrenia. Sustained attention on high-load information-processing tasks, in particular, has been shown to remain stably impaired throughout late childhood and adolescence in those who go on to develop schizophrenia.[36]

It is important to recognize that increasing interest has developed in applying similar endophenotypic or genetic HR strategies to the risk and neuropsychological vulnerability for affective psychoses, especially bipolar (BP) disorder.[37] This HR literature is much smaller but is growing. Schizophrenia and affective psychoses have traditionally been considered nonoverlapping illnesses.[8] However, more recent studies of BP psychoses have suggested that there are some overlapping genes that may create similar neurobiological susceptibilities,[38–40] a development consistent with calls for identifying the commonalities and differences among the psychoses.[1] At present, the literature is more developed in the area of BP than unipolar psychotic disorders. Some limited data also suggest that patients with chronic BP psychoses have somewhat similar but milder neuropsychological profiles than patients with schizophrenia.[41] Within some cognitive domains, however, such as spatial working memory, impairments in BP patients have not been documented to date.[42,43]

In contrast to the picture in schizophrenia, most studies of families of adults with affective psychosis, including twin studies, have not observed robust differences

Table 1. Neuropsychological Performance in Persons (Age < 30) at Genetic Risk for Schizophrenia

Neuropsychological Function and Cognitive Tasks	Significance	Reference
Attention Functions		
Perceptual-Motor Speed		
Digit Symbol/Coding	+	Mednick and Schulsinger (1968)[91]
	+	Landau et al. (1972)[92]
	+	Byrne et al. (2003)[78]
	+	Niendam et al. (2003)[79]
	−	Asarnow et al. (1978)[93]
Reaction Time—simple and warned	+	Schreiber et al. (1992)[94]
Reaction Time—crossover effect	+	Maier et al. (1994)[95]
Reaction Time—modality shift effect	−	Maier et al. (1994)[95]
Reaction Time	−	Schubert and McNeil (2005)[51]
Spokes Test (B)	+	Asarnow et al. (1978)[93]
Stroop	−	Asarnow et al. (1978)[93]
	+	Byrne et al. (2003)[78]
Trail Making	−	Schubert and McNeil (2005)[51]
Visual Cancellations (Omissions)	+	Lifshitz et al. (1985)[96]
	+	Schreiber et al. (1992)[94]
Visual Search	+	Winters et al. (1981)[97]
Short-Term or Working Memory		
Arithmetic	+	Mednick and Schulsinger (1968)[91]
	+	Landau et al. (1972)[92]
	±	Byrne et al. (1999)[77] (only in males)
Thurstone Number Facility	+	Sohlberg (1985)[98]
Thurstone Number Series	+	Sohlberg (1985)[98]
Attention Span Test	±	Erlenmeyer-Kimling and Cornblatt (1978)[99] (only on the 5-letter sequence with fast rate of presentation)
Auditory Constant Trigrams	+	Rutschmann et al. (1980)[100]
Digit Span (with distraction)	+	Cornblatt and Erlenmeyer-Kimling (1985)[50]
	+	Harvey et al. (1981)[101]
Digit Span	−	Mednick and Schulsinger (1968)[91]
	−	Lifshitz et al. (1985)[96]
	−	Cosway et al. (2000)[76]
	−	Niendam et al. (2003)[79]
	−	Schubert et al. (2005)[51]
Dichotic Listening	−	Asarnow et al. (1978)[93]
	−	Orvaschel et al. (1979)[102]
	+	Hallett et al. (1986)[103] (abnormal asymmetry)
Information Overload	+	Cornblatt and Erlenmeyer-Kimling (1984)[104]
Intentional Learning	+	Driscoll (1984)[105] (with distraction)
Working Memory Span		
Counting Span	+	Davalos et al. (2004)[35]
Sentence Span	+	Davalos et al. (2004)[35]
Hayling Sentence Completion Test, Section A Time	+	Byrne et al. (2003)[78]
Vigilance and Sustained Attention		
Simple CPTs	−	Grunebaum et al. (1974)[106] (6 year olds)
	−	Asarnow et al. (1977)[107]
	−	Cohler et al. (1977)[108] (small sample)
	−	Rutschmann et al. (1986)[109]
	−	Nuechterlein (1983)[110]
Difficult CPTs		
"X" task (colors)	+	Grunebaum et al. (1974)[106] (difficult for 5 year olds)
Degraded Stimulus CPT	+	Nuechterlein (1983)[110]
Playing Card CPT	+	Rutschmann et al. (1977)[111] (difficult for < 11 year olds)
	+	Erlenmeyer-Kimling and Cornblatt (1992)[112]
Double Digit CPT	+	Rutschmann et al. (1986)[109] (ages 7–12)
CPT-IP	+	Erlenmeyer-Kimling and Cornblatt (1982)[113]
	+	Cornblatt et al. (1992)[86]
	−	Cosway et al. (2002)[85]
Other Attention Tasks		
Selective Attention	+	Schubert and McNeil (2005)[51]
Stop Task	+	Davalos et al. (2004)[35]

Table 1. Continued

Neuropsychological Function and Cognitive Tasks	Significance	Reference
Span of Apprehension	+	Asarnow et al. (1978)[93] (10 elements only)
Executive Functions		
Concept Formation and Abstraction		
Concept Attainment	+	Asarnow et al. (1978)[93]
Object Sorting Test	+	Winters et al. (1981)[97]
	−	Neale (1982)[114] (trend for deviant subgroup)
Picture Arrangement	+	Niendam et al. (2003)[79]
Wisconsin Card Sort	+	Wolf et al. (2002)[115]
	−	Schubert and McNeil (2005)[51]
Verbal-Linguistic Ability		
Comprehension	−	Niendam et al. (2003)[79]
Grammatical Reasoning	+	Schubert and McNeil (2005)[51]
Information	−	Niendam et al. (2003)[79]
NART Reading	+	Byrne et al. (2003)[78]
Speech Sounds Perception	+	Hallett and Green (1983)[116]
Token Test	+	Byrne et al. (2003)[78]
Verbal Fluency	−	Schubert and McNeil (2005)[51]
FAS	−	Byrne et al. (2003)[78]
Category Fluency	+	Byrne et al. (2003)[78]
WAIS-R Vocabulary	+	Byrne et al. (2003)[78]
WISC Vocabulary	+	Niendam et al. (2003)[79]
	+	Davalos et al. (2004)[35]
Thurstone Verbal Memory	−	Sohlberg (1985)[98]
Thurstone Word Grouping	−	Sohlberg (1985)[98]
Thurstone Letter Series	+	Sohlberg (1985)[98]
Visual-Spatial Ability		
Block Design	+	Cosway et al. (2000)[76]
	−	Niendam et al. (2003)[79]
	−	Davalos et al. (2004)[35]
	−	Schubert and McNeil (2005)[51]
Paper Folding	−	Davalos et al. (2004)[35]
Thurstone Spatial Relations	+	Sohlberg (1985)[98]
Bender Gestalt	−	Sohlberg (1985)[98]
Taylor Perceptual Closure Test	+	Sohlberg (1985)[98]
General Intelligence (IQ)		
Full-Scale or Estimate	±	Rieder et al. (1977)[117]
	+	Neale et al. (1984)[114]
	±	Goodman (1987)[118] (youngest group only)
	+	Schreiber et al. (1992)[94] (especially VIQ)
	+	Dworkin et al. (1993)[119]
	+	Byrne et al. (2003)[78]
	+	Cannon et al. (2000)[120]
	+	Goldstein et al. (2000)[49]
	−	Klein and Salzman (1984)[121]
	−	Worland et al. (1984)[122]
	−	Sameroff et al. (1984)[123]
	−	Sohlberg and Yaniv (1985)[124] (Raven's Matrices)
	−	Sohlberg (1985)[98]
Declarative Memory		
Verbal Story and List Recall		
Story Recall with Distraction	+	Lifshitz et al. (1985)[96]
Rey Auditory Verbal Learning	+	Byrne et al. (2003)[78]
Rivermead Story	+	Byrne et al. (2003)[78]
Word Pairs Test	+	Schubert and McNeil (2005)[51]
Visual Recall		
Memory for Designs	−	Orvaschel et al. (1979)[102]
Visual Reproductions	+	Byrne et al. (2003)[78]
Motor Function		
Individual Rhythm	−	Lifshitz et al. (1985)[96]
Mirror Drawing	+	Lifshitz et al. (1985)[96]

Table 1. Continued

Neuropsychological Function and Cognitive Tasks	Significance	Reference
Finger Tapping	−	Schubert and McNeil (2005)[51]
Cerebral Asymmetry		
Story Comprehension and Recall	+	Hallet and Green (1983)[116] (impaired binaural)
	+	Hallet et al. (1986)[103]
Verbal Dichotic Listening	−	Hallet et al. (1986)[103]
Handedness	+	Hallet and Green (1983)[116]
	−	Byrne et al. (1999)[77]

Note: + indicates $p < .05$, genetic risk for schizophrenia group differed significantly from a control group; ± = mixed results, with at least one significant difference between groups on a number of scores from the same test; – indicates $p > .05$, no significant differences between the genetic high risk and control group.

compared to controls.[43–47] However, Ferrier et al.[48] reported impairments on verbal and visual span tasks in relatives of BP patients. In genetic HR studies of children, the Harvard birth cohort study[49] did not find significant IQ deficits in HR-AFF children. Cornblatt and Erlenmeyer-Kimling[50] found some degree of attentional deficits in those at HR-AFF, but it was of smaller magnitude and less stable than that seen in HR-SCZ offspring. Schubert and McNeil[51] detected more neuropsychological impairment in young adults at HR-SCZ than HR-AFF but found comparable impairment between groups in grammatical reasoning. Thus, the extant literature suggests weaker neurocognitive impairments in HR-AFF than HR-SCZ. Nevertheless, more research is needed to clarify the neurocognitive associations with HR-AFF and to identify what may be specific to HR-SCZ.

Exploring neuropsychological differences in HR relatives during adolescence is an important strategy for at least 2 reasons. First, because it has been hypothesized that HR subjects may be undergoing critical neuromaturational changes during adolescence,[52–54] intensive studies during this period could provide clues about the pathophysiology and/or premorbid predictors of psychosis. Second, because the period of maximal risk for psychosis occurs during ages 20–30, studies beginning shortly before this period, during the teen years, could allow active assessment into the period when approximately 5–10% of genetically HR subjects are likely to develop illness. In contrast, studies beginning in early childhood have the complexity and financial expense of a 15–25 year interval before participants enter the period of highest risk.[55] Studying premorbid differences holds the potential to identify predictors of illness and inform targets for prevention or early intervention.[56]

To enhance statistical power and generalizability, this study combined baseline data from 2 genetic HR studies that employed reasonably comparable ascertainment and assessment methodologies: the Harvard Adolescent High Risk Study (HAHRS) and the Hillside Family Study (HFS). Moreover, as both studies have ascertained small samples at HR for affective psychoses, combining the samples allowed the creation of a modest sample of HR-AFF to test specificity of neurocognitive deficits for types of psychosis. Two primary hypotheses guided our analyses. First, participants at HR for schizophrenia would be significantly impaired in their neuropsychological profile compared to community controls. Based on the literature, we predicted that persons at HR for schizophrenia would be significantly impaired compared to controls on 4 dimensions: verbal ability, verbal declarative memory, executive function/working memory, and sustained attention. Second, in a more exploratory vein (due in part to limited sample size and power), we hypothesized that participants at HR for affective psychosis would fall intermediate, between people at HR for schizophrenia and controls, in these same domains of neurocognitive functioning.

Method

Harvard Adolescent High Risk Study

Data collected in the HAHRS were ascertained from the metropolitan Boston area between 1998 and 2004 (MH 43518; Tsuang and Seidman, PI). The subjects of this study comprised 3 groups: biological children and siblings of schizophrenia patient probands (HR-SCZ), biological children and siblings of affective psychosis patient probands (HR-AFF), and biological children and siblings of community control subject probands (CC). All HR and CC participants were between the ages of 13 and 25 at the time of their neurocognitive assessments. The HR-SCZ group consisted of 35 children and siblings of 26 adult probands who were diagnosed according to DSM-IV criteria[57] with either schizophrenia (n = 22) or schizoaffective disorder, depressed type (n = 4), using the Diagnostic Interview for Genetic Studies (DIGS)[58] and the Family Interview for Genetic Studies (FIGS).[59] Twenty-nine HR-SCZ were relatives of

persons with schizophrenia and 6 of persons with schizoaffective disorder, depressed type. Seventeen of the schizophrenia probands had diagnoses of paranoid schizophrenia (with 20 HR-SCZ), and 5 had diagnoses of undifferentiated schizophrenia, including one whose other parent had schizoaffective disorder, depressed type (with 9 HR-SCZ). The HR-AFF group consisted of 6 children and siblings of 4 adult probands who were diagnosed according to DSM-IV criteria with either bipolar disorder with psychotic features (n = 2), schizoaffective disorder, bipolar type (n = 1), or major depression with psychotic features (n = 1). The probands were ascertained through hospitals and outpatient clinics in and around Boston.

The community control group consisted of 54 children of 34 control parent probands. The parents were diagnosed according to DSM-IV criteria with no mental illness (n = 24), major depressive disorder (n = 8), mood disorder due to a general medical condition (n = 1), or cannabis abuse (n = 1), using the DIGS and FIGS. The adult control probands were drawn from respondents to local newspaper advertisements and announcements posted in the sites from which HR-SCZ probands were recruited. The children and siblings of both sets of probands were subsequently ascertained through their related adult probands to determine their eligibility, availability, and willingness to participate as subjects in the study.

HR participants were excluded if they had any lifetime diagnosis of psychotic illness, substance dependence, or neurological disease, a history of head injury or medical illness with documented cognitive sequelae, sensory impairments, current psychotropic medication use, or a full-scale IQ estimate of less than 70. Participants in the control group were screened with the same criteria, with an additional exclusion criterion of any first- or second-degree biological relatives with lifetime history of a psychotic disorder.

Offspring and siblings of control and schizophrenia probands were screened for presence of psychosis with the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS).[60] The Psychosis, Mood Disorders, and Substance Abuse modules of the WASH-U-KSADS were administered along with a Neurodevelopmental Questionnaire (a rating scale which has excellent reliability—intraclass correlations above 0.95) to establish other inclusion and exclusion criteria.

Subjects 18 and older gave informed consent, while subjects younger than 18 years of age gave assent in conjunction with informed consent provided by a parent. Subjects received an honorarium for participating. The study was approved by the human research committees of the Massachusetts Mental Health Center, Massachusetts General Hospital, Harvard Medical School, and other recruitment sites.

Hillside Family Study

Data collected in the HFS were ascertained from the metropolitan New York area between 1995 and 2001 (Cornblatt, PI). The study was conducted at 2 sites, the Elmhurst Hospital Center in Jackson Heights, NY, between July 1, 1995 and July 1, 1996, and the Zucker Hillside Hospital at the Long Island Jewish Medical Center in Glen Oaks, NY, between July 1, 1996, and June 30, 2001. The subjects of this study comprised 3 groups: 38 biological siblings of 29 schizophrenia patient probands, 12 biological siblings of 11 affective psychosis patient probands, and 63 biological siblings of 49 control subject probands. The schizophrenia sample consisted of patients with the following diagnoses: undifferentiated type (n = 10), paranoid type (n = 7), disorganized type (n = 3), schizoaffective disorder (n = 8), and schizophreniform disorder (n = 1). All HR participants were between the ages of 12 and 22 at the time of ascertainment and testing. Patient probands were diagnosed according to the same criteria as in HAHRS for a current DSM-IV Axis I diagnosis of schizophrenia, any subtype, schizoaffective disorder (depressed subtype), or mood disorder with psychosis at the time of ascertainment and enrollment. HFS patient probands were primarily recruited from the adolescent inpatient units at Elmhurst Hospital and the Zucker Hillside Hospital in Queens, NY.

HFS participants who served as control subjects were recruited in 2 ways: (1) by study staff using a modified acquaintanceship method (ie, siblings of probands were asked to refer friends, which yielded 4 participants); and (2) as part of a department-wide effort to recruit control subjects that included newspaper advertisements and community flyers. The diagnostic exclusion criteria for CC and HR participants were the same as in the HAHRS, including no family history of psychosis for CC. The nonpsychotic siblings of probands were subsequently ascertained through their related probands to determine their eligibility and willingness to participate in the study.

HFS diagnostic procedures included standard administration of the Kiddie Schedule for Affective Disorders and Schizophrenia, Epidemiologic Version for DSM-IV (K-SADS-E)[61] to parents and probands in separate interviews. Interviewers were at the master's level (or equivalent, relevant professional experience) and trained in the use of the K-SADS-E in consultation with Dr Orvaschel. Both parental and proband report of history and symptoms, as well as all available clinical information (typically from inpatient evaluation and treatment records), were used to make diagnoses. Consensus ratings on all Axis I diagnoses were made with Dr Jeremy Silverman, Ph.D., a study-independent consulting expert diagnostician experienced with family studies of schizophrenia and schizotypal personality disorder. Dr Silverman met with interviewers after the interview was completed,

reviewed a detailed report of the interview, and confirmed or altered the diagnosis assigned by the study interviewer. Local institutional review boards (IRB) approved the projects conducted at their site. IRB assent and consent procedures were comparable to the HAHRS.

Combined Study Sample

The principal investigators (Drs Seidman and Cornblatt) obtained IRB permission from their respective sites to combine data from the sites after removing any identifying information. The final de-identified samples were created by combining data from the 2 studies after excluding a number of subjects because of missing data (detailed below). Neuropsychological test performance data were available for 208 participants: 73 HR-SCZ, 18 HR-AFF, and 117 "low-risk" CC. Secondary analyses contained a smaller sample of controls to better equate groups on demographics (see data analysis below). All participants were English-speaking and between the ages of 12 and 25.

Neuropsychological Measures

Each study site contained distinct and overlapping tests in their neuropsychological battery. Of the 22 measures administered by the HAHRS and the 26 measures administered by the HFS, 10 tests were regarded as sufficiently comparable in terms of their administration and scoring procedures to be included in data combination and analyses. To facilitate the interpretation of results, differences in test forms and administration procedures between study sites for these tests are described.

Both sites administered 4 subtests from different versions of the Wechsler Intelligence Scales, including Vocabulary, Block Design, Digit Span, and Digit Symbol. Both sites employed the Wechsler Intelligence Scale for Children—Third Edition (WISC-III)[62] when assessing youth (HAHRS $<$ 17 years old; HFS $<$ 16 years old). The HAHRS used the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III)[63] for participants age 17 and older, while the HFS, having been initiated earlier, employed the Wechsler Adult Intelligence Scale–Revised (WAIS-R)[64] version of these subtests for participants age 16 and older. Both sites employed the Wide Range Achievement Test—Revision 3 (WRAT-3)[65] Reading subtest; however, the HAHRS used the Blue form for all participants, while the HFS alternated its use of Blue and Tan forms.

Both sites used the same model of the Grooved Pegboard (Lafayette Model 32025), with minor differences in administration procedures. Regarding the computer-administered Continuous Performance Test—Identical Pairs (CPT-IP),[66] the HAHRS used extended trials of the shapes and 4-digit conditions (ie, 300 of each instead of the more standard 150 trials), while the HFS administered its standard battery in addition to other conditions. Thus, only the first 150 trials of each condition (which were the initial trials in both tests at both sites) were included for the purpose of combining and analyzing data. Stimulus presentation and interstimulus interval times were equivalent, as were other standard task administration procedures. (Dr Cornblatt was a consultant to the HAHRS from the beginning of the study for the CPT-IP to ensure comparability between sites.) For the Trail Making Test (TMT), both Parts A and B were administered in standard fashion by both study sites,[67] and time to completion was recorded; however, the HAHRS used the Adult version of the task for all participants, while the HFS used the Intermediate version of the TMT for participants younger than 15 years old. Data from the TMT Parts A and B were combined by creating z-scores for each subgroup based on site- and age-specific control subjects.

For the domain of verbal declarative memory, the sites employed different versions of story memory measures. The HAHRS used Logical Memory I and II subtests from the Wechsler Memory Scale—Third Edition (WMS-III)[68] for participants 17 years or older and the Story Memory (Immediate and Delayed) subtests from the Children's Memory Scale (CMS)[69] for participants age 13–16. Given that the HFS study was initiated earlier, the HFS used the Logical Memory I and II subtests from the Wechsler Memory Scale—Revised (WMS-R)[70] for all subjects. Each measure requires administration of 2 stories. However, the WMS-III requires a second administration of its second story, and the WMS-R/III and CMS make use of stories with a different number of total "units" for which raw score credit can be earned. To maximize comparability of measurement across studies, only the immediate recall condition for each story (heard the first time) was included in the data combination. Moreover, since the adult and child tests present a different number of story details, participants' total raw scores on each measure were calculated as a percentage of story units recalled from both stories ("percentage recalled").

Lastly, each study site employed a slightly different version of the Controlled Oral Word Association test (COWA), a measure of phonemic verbal fluency. The HAHRS employed the letters FAS[71] in its administration of the test, while the HFS used PRW or CFL[72] in alternating fashion. Despite these differences, it was regarded as reasonable to combine the data between sites for 3 reasons: administration procedures were entirely equivalent; the PRW and CFL conditions were designed to be comparable; and the few studies that have been conducted comparing the PRW/CFL conditions to the FAS condition in psychiatric and nonpsychiatric samples generally document little difference between them.[73]

Data Analyses: Multivariate Data Reduction of Neuropsychological Measures

The 13 scores from the 10 tests used in this study were combined into 6 summary domains, using a similar grouping structure for domains that have been used in studies focusing on adult relatives of patients with schizophrenia.[74] The 13 variables were standardized using the means and standard deviations of the CC group, which resulted in z-scores with the CC having a mean of 0 and a standard deviation of 1. The variables were then organized as unweighted linear combinations into the 6 neurocognitive domains: Verbal Ability (based on the average of the WRAT-3 Reading and Wechsler Vocabulary z-scores), Visual-Spatial Ability (consisting of Wechsler Block Design), Verbal Memory (consisting of the Logical or Story Memory I immediate story recall percentage), Executive Functioning/Working Memory Functioning (composed of Trail Making Test B time to completion, total words generated on the Controlled Oral Word Association test, Wechsler Digit Symbol and Digit Span subtest z-scores divided by 4), Motor Functioning (based on the average of Trail Making Test A time to completion and the Grooved Pegboard Right and Left z-scores), and Sustained Attention (consisting of the average of the 2 CPT-IP z-scores).

Final Sample Composition

After deletion of 6 cases with greater than 50% missing data on neurocognitive measures, the majority (87.9%) of the remaining 208 cases in the combined data set had complete data on all 13 individual neurocognitive variables. Preliminary analyses comparing groups on demographics using this sample revealed that there were significant differences on age and parental education in which controls were younger ($F_{(2,205)} = 5.13$, $p = .007$) and their parents were significantly more educated ($F_{(2,205)} = 12.3$, $p < .001$) than HR groups. In testing the effects of age and parental education on neuropsychological outcomes, age had minor effects on statistical significance, but not surprisingly, parental education had a highly significant attenuating effect on group differences. Given the fact that we initially had a large control group (n = 117), we chose to systematically delete the controls with the highest parental education in order to demographically match controls with HR participants. Our criteria included the goal of maintaining matching on other demographics (eg, sex), reasonable parity between the 2 sites in regard to percentage of controls excluded from the sites, and blindness to the level of neuropsychological performance. We deleted 33 CCs, leaving a control group (n = 84) roughly comparable to the total number of HR participants (n = 91). Although our deletion strategy took into account the contributions of the 2 sites such that we attempted to delete equal percentages, we retained a slightly higher percentage of CCs from the HFS site (77.8%) than the HAHRS site (64.8%). Finally, because a subset of CCs (n = 12) had a parent with a history of depression that could potentially affect neurocognitive functioning, we compared groups with and without these subjects.

Replacement of Missing Data

Because a small amount of data was missing on some neuropsychological tests (2.4% overall), with the highest percentage on the only computerized test, the CPT-IP (with 6.9–8.0% missing on the shapes and digits trials, respectively), data imputation methods were employed to control case deletion in multivariate analyses. Data were imputed by individually regressing the incomplete variables on predictors including demographic variables (ie, age, sex, and mean parental education), Vocabulary and Block Design scaled scores, and related variables (based on significant bivariate correlations). Nine subjects were missing parental education data (7 from the HR-SCZ group and 1 each from the HR-AFF and CC groups), and these were replaced by the group mean.

Statistical Analyses

Continuously distributed demographic variables, including age, education, and mean parental education (calculated as the average of both parents' highest years of education completed or a parent's highest level of education completed in those cases with only 1 parent's level of education available), were compared between high-risk and control groups and across study sites using 2-way analysis of variance, while categorical demographic variables, including sex, handedness, and ethnicity, were compared between the groups using chi-square tests. In addition, site was entered in the initial models to examine site difference effects on the neurocognitive variables. While there were significant site effects for a few tests, there were no group by site interactions, and site was thus dropped from subsequent analyses to maintain optimal statistical power and simplify the presentation of results.

Comparison of the 3 groups on overall neuropsychological functioning was conducted by using multivariate analysis of variance (MANOVA) followed by analysis of covariance (MANCOVA). Although group matching eliminated significant group differences on age and parental education, we continued to test effects controlling for these variables, as they are associated with neurocognitive functioning. The 6 cognitive domain scores were subsequently analyzed by analysis of variance (ANOVA). Analyses addressed the nonindependence of observations within families by adjusting variance estimates using a mixed model procedure (PROC MIX) in Statistical Analysis System (SAS) Version 8.01 that assumed that the covariance within a family is the same for each family member (ie, compound symmetry) with Huber's

(1967) formula,[75] a theoretical bootstrap procedure that computes accurate estimates of variance for clustered data. This method enters cluster scores (ie, the sum of scores within families) instead of individual scores into the formula for the estimate of the variance in the general linear model. Univariate analyses of individual domains and test scores followed the same procedures as above, controlling for nonindependence of observations within families. Statistical significance was set at $p < .05$ using 2-tailed tests. Effect size estimates were calculated with Cohen's d (mean of the control group minus mean of the HR group divided by the pooled standard deviation).

Results

Demographic Characteristics

As Table 2 shows, comparing HR participants with CCs revealed no significant group differences ($p > .05$) in either site or in the combined sample, and there were no site by group interactions on any of the demographic variables (ie, age, education, sex, ethnicity, handedness, or parental education). There were site differences in that HFS participants had significantly more parental education than HAHRS participants. Because we were interested in maximizing power by assessing the combined sample, we did not enter site into the analyses of neuropsychological data that are presented. However, we controlled for parental education and age. Demographic characteristics are summarized in Table 2.

Neuropsychological Functioning (Overall Profile Analysis)

As Table 3 shows, results of MANOVA revealed that, compared with the CC group, the HR-SCZ group was significantly impaired in the neurocognitive domains, while the HR-AFF group showed a trend toward neurocognitive

Table 2. Demographic Characteristics of HR-SCZ, HR-AFF, and CC Groups

	Total Sample				
	HR-SCZ (n = 73) Mean (SD)	HR-AFF (n = 18) Mean (SD)	CC (n = 84) Mean (SD)	Test Statistic	p
Age	18.1 (3.5)	17.7 (3.7)	16.9 (3.2)	F = 2.03	.135
Subject Education	10.8 (2.4)	11.2 (3.6)	10.9 (2.9)	F = .066	.937
Parental Education	13.2 (2.8)	13.8 (3.7)	14.2 (2.4)	F = 2.65	.073
Female (%)	42 (57.5%)	14 (77.8%)	47 (56.0%)	$\chi^2 = 3.01$	.222
Caucasian (%)	38 (52.1%)	11 (61.1%)	42 (50.0%)	$\chi^2 = .733$	.693
Right-handed (%)	61 (83.6%)	16 (88.9%)	72 (85.7%)	$\chi^2 = 2.12$	.715
	Harvard Adolescent High Risk Study				
	HR-SCZ (n = 35) Mean (SD)	HR-AFF (n = 6) Mean (SD)	CC (n = 35) Mean (SD)	Test Statistic	p
Age	19.1 (3.8)	17.6 (3.6)	17.7 (4.0)	F = 1.13	.328
Subject Education	10.9 (2.5)	9.8 (3.3)	11.3 (3.4)	F = .627	.537
Parental Education	12.7 (2.7)	11.2 (4.3)	13.5 (2.7)	F = 1.94	.151
Female (%)	20 (57.1%)	4 (66.7%)	20 (57.1%)	$\chi^2 = 1.09$	.579
Caucasian (%)	20 (57.1%)	3 (50.0%)	20 (57.1%)	$\chi^2 = .044$	.978
Right-handed (%)	31 (88.6%)	5 (83.3%)	30 (85.7%)	$\chi^2 = 2.60$	.627
	Hillside Family Study				
	HR-SCZ (n = 38) Mean (SD)	HR-AFF (n = 12) Mean (SD)	CC (n = 49) Mean (SD)	Test Statistic	p
Age	17.1 (2.9)	17.7 (3.9)	16.3 (2.3)	F = 2.42	.174
Subject Education	10.7 (2.3)	11.8 (3.7)	10.5 (2.4)	F = 1.29	.280
Parental Education	13.7 (2.8)	14.7 (3.1)	14.6 (2.2)	F = 1.62	.204
Female (%)	22 (57.9%)	10 (83.3%)	27 (55.1%)	$\chi^2 = 2.03$	.362
Caucasian (%)	18 (47.4%)	8 (75.0%)	22 (44.9%)	$\chi^2 = 1.14$	.566
Right-handed (%)	30 (78.9%)	11 (91.7%)	42 (85.7%)	$\chi^2 = .822$	.935

Note: HR-SCZ = genetic high-risk for schizophrenia; HR-AFF = genetic high-risk for affective psychosis; CC = community control. For the Total Sample analyses, there is a site effect for parental education (F = 11.78, p = .001). There were no other significant site or group by site interactions.

Table 3. Overall Neurocognitive Functioning Between Groups: Multivariate Comparisons With and Without Covarying (on Group Only) Age and Parental Education

	HR-SCZ vs CC			HR-AFF vs CC			HR-SCZ vs HR-AFF		
Group Comparison	F	df	p	F	df	p	F	df	p
Group	5.80	6/150	<.001	1.81	6/95	.106	.516	6/82	.795
Study Site	3.01	6/148	.008	2.19	6/93	.051	2.14	6/82	.058
Group × Site	.951	6/148	.461	.920	6/93	.485	.992	6/82	.436
Group Effects After Covariates									
Age	6.31	6/149	<.001	1.73	6/94	.123	.687	6/83	.661
Parental Education	4.70	6/149	<.001	1.82	6/94	.104	.494	6/83	.811
Age and Parental Education	5.05	6/148	<.001	1.65	6/93	.142	.647	6/82	.692

Note: HR-SCZ = genetic high-risk for schizophrenia; HR-AFF = genetic high-risk for affective psychosis; CC = community controls.

impairment. There were no significant differences between HR-SCZ and HR-AFF groups across neurocognitive domains. These results remained significant when covarying age and mean parental education.

Neuropsychological Functioning (Specific Domain and Individual Test Analyses) for n = 84 Community Control Sample

Table 4 displays means and standard deviations for the 6 neurocognitive factors (in z-score units), and means and standard deviations for individual test scores by group (in their original metric based on original, nonimputed data, so n's are reduced slightly for the individual test score analyses). As Table 4 and Figure 1 show, compared with controls, participants at HR-SCZ were significantly impaired in Verbal Ability (d =.73) and Executive Functioning/Working Memory (d =.47). Performance was nonsignificantly poorer in Verbal Memory (d = .27) and Visual-Spatial Ability (d =.22). The HR-SCZ and CC groups were virtually identical on the Motor (d = .03) and Sustained Attention (d = .08) domains. Performance between groups on the individual component tests in the Verbal Ability domain, the WRAT-3 Reading and Wechsler Intelligence Scale Vocabulary subtests, and the verbal fluency test of the Executive Functioning/Working Memory domain was significantly lower in the HR-SCZ group than in CCs.

Compared with controls, participants at HR-AFF were significantly impaired only in the Verbal Ability domain (d = .64). At the individual test level, HR-AFF participants were impaired on the Vocabulary (d =.73) and Digit Span (d = .47) subtests, and marginally better (p = .063) than CCs on the Digit Symbol subtest (d = .51).

There were no significant domain differences between HR-SCZ and HR-AFF groups; however, at the individual test level the HR-AFF group performed significantly better than the HR-SCZ group on the Digit Symbol subtest (d = .79).

Neuropsychological Functioning for n = 72 Community Control Sample

Analyses used parental education and age as covariates (parental education was significantly higher in CCs after excluding controls with a parent with a diagnosis of depression: $F_{(2,160)} = 3.49$, p = .033). Compared with CCs, HR-SCZ remained significantly different on Verbal Ability (d =.84) and Executive Functioning/Working Memory (d =.54) (see Table 5). In addition, members of the HR-SCZ group performed significantly lower on Verbal Memory (d =.39) and marginally less well on Visual-Spatial Ability (p = .061). Consistent with prior analyses, individuals at HR-AFF performed significantly lower on Verbal Ability than CCs (d =.76). Although the HR-AFF individuals were not significantly lower than controls on overall Executive Functioning/Working Memory, they were now significantly lower on Digit Span performance (d = .53).

Discussion

As predicted, HR-SCZ subjects were significantly impaired on neuropsychological functioning compared with low-risk community controls after statistically adjusting for age, parental education, and correlated data within families. HR-AFF participants showed slightly less impairment overall but were not significantly different when compared with HR-SCZ. Those at HR-SCZ demonstrated an overall difference in neurocognitive function, marked especially by impairments in Verbal Ability and Executive Functioning/Working Memory. HR-AFF showed reliable deficits in Verbal Ability only, and there were no significant differences between the high-risk groups at the domain level, though the HR-SCZ group performed worse than the HR-AFF group on the Digit Symbol/Coding task. HR-SCZ performed significantly worse than controls in Verbal

Table 4. Neurocognitive Domain and Individual Test Scores Among High-Risk and Community Control (n = 84) Groups

Domain[a]/Individual Test Variable[b]	HR-SCZ (1)		HR-AFF (2)		CC (3)		Pairwise Comparisons[c]					
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	1–2	d[d]	1–3	d[d]	2–3	d[d]
Verbal Ability	73	−.64 (.77)	18	−.51 (1.24)	84	0.0 (.91)	.661	.09	**<.001**	.73	**.015**	.64
WRAT-3 Reading SS	73	99.5 (11.4)	18	101.9 (17.5)	84	107.2 (11.6)	.602	.14	**<.001**	.57	.102	.44
Vocabulary ScS	73	9.2 (2.6)	18	9.4 (3.7)	83	11.3 (3.5)	.841	.02	**<.001**	.73	**.005**	.73
Visual-Spatial	73	−.22 (.66)	18	−.19 (1.03)	84	0.0 (1.00)	.961	.02	.179	.22	.421	.24
Block Design ScS	72	9.4 (2.4)	18	9.4 (3.6)	83	10.1 (3.5)	.961	.02	.179	.22	.421	.24
Verbal Memory	73	−.24 (.97)	18	.04 (.93)	84	−.001 (1.00)	.321	.28	.067	.27	.978	.01
Story Recall Percentage	72	.47 (.13)	18	.50 (.13)	84	.50 (.13)	.321	.28	.067	.26	.978	.01
Executive Functioning/ Working Memory	73	−.31 (.64)	18	−.09 (.64)	84	0.0 (.74)	.207	.31	**.006**	.47	.540	.16
COWA Raw Score	73	34.2 (10.8)	18	35.2 (11.5)	84	37.4 (10.9)	.780	.08	**.034**	.37	.271	.29
Digit Span ScS	73	10.3 (2.9)	18	9.6 (2.2)	82	11.0 (3.4)	.326	.25	.158	.22	**.047**	.47
Coding/Digit Symbol ScS	72	9.2 (2.9)	18	11.5 (2.9)	82	10.0 (3.0)	**.004**	.79	.067	.29	.063	.51
TMT-B (sec)	73	65.9 (25.0)	18	60.3 (31.7)	83	58.8 (36.3)	.558	.12	.347	.13	.831	.01
Motor	73	.02 (.85)	18	−.04 (1.13)	84	.01 (.72)	.967	.10	.844	.03	.643	.07
Grooved Pegboard R (sec)	69	71.7 (17.7)	18	73.2 (17.9)	79	70.6 (13.5)	.847	.13	.709	.06	.395	.19
Grooved Pegboard L (sec)	69	78.3 (19.1)	18	75.2 (19.4)	79	78.7 (16.8)	.556	.15	.603	.10	.415	.24
TMT-A (sec)	73	27.2 (8.5)	18	27.5 (12.9)	83	27.6 (12.4)	.568	.08	.312	.15	.643	.06
Sustained Attention	73	−.0007 (.76)	18	.22 (.79)	84	0.0 (.92)	.296	.30	.668	.08	.534	.21
CPT-IP Digits d'	66	1.6 (.92)	18	1.8 (.76)	77	1.6 (1.01)	.473	.20	.706	.09	.641	.11
CPT-IP Shapes d'	66	1.7 (.83)	18	1.9 (.90)	79	1.7 (.97)	.271	.33	.674	.08	.490	.25

Note: HR-SCZ = genetic high-risk for schizophrenia; HR-AFF = genetic high-risk for affective psychosis; CC = community controls.
[a]Neurocognitive domain scores are z-scores.
[b]Individual test scores reflect the actual number of subjects prior to the imputation of missing data. WRAT-3 score is a standard score (SS); subtests of the WISC-III/WAIS-R/WAIS-III (Vocabulary, Block Design, Coding/Digit Symbol) are (age-corrected) scaled scores (ScS); Story Recall Percentage is the percentage of units recalled on immediate recall condition for CMS Stories/WMS-R and WMS-III Logical Memory I; COWA (Controlled Oral Word Association test) is a raw score (total words generated); Grooved Pegboard and TMT raw scores are in seconds; CPT-IP values are d'.
[c]1–2 = HR-SCZ vs HR-AFF; 1–3 = HR-SCZ vs CC; 2–3 = HR-AFF vs CC, controlling for subject age, mean parental education, and correlated data in a mixed model; statistically significant comparisons ($p < .05$) are in boldface.
[d]d = Cohen's d based on least squared means, controlling for subject age and mean parental education.

Memory and marginally worse in Visual-Spatial functions in analyses modified by excluding subjects who had parents with diagnoses of depression. The effects for these differences were large for Verbal Ability ($d > .70$) and medium for Executive Functioning/Working Memory, Visual-Spatial Ability, and Verbal Memory ($d = .30$ to .54). Surprisingly, and contrary to our a priori hypothesis, this study found no group differences on the CPT-IP; the CPT-IP had been identified as a robust indictor of genetic risk for schizophrenia in several prior studies[26] with the notable exception of the Edinburgh HR study.[76]

Neuropsychological Functioning in HR-SCZ

Based on prior genetic HR studies, the impairments in verbal-linguistic functions are expected for those at HR-SCZ. A number of recent studies have documented impairments in verbal expressive functions such as Vocabulary or single word reading,[35,77–79] and adult relatives also tend to be impaired on WRAT-3 Reading ($d = .50$).[26] At the same time, it is important to note that our HR groups' mean Vocabulary and WRAT-3 Reading standard scores were in the average range and do not necessarily represent clinically significant impairments in most subjects. The difficulty in verbal fluency has been less frequently studied in HR children, but it has a robust effect size in adult relatives ($d = .48$), and it is one of the most severe impairments in patients with schizophrenia.[7] Reduced ability to access semantic information storage systems with normal efficiency is typically regarded as the basis of this deficit.[80] In addition, a number of other HR studies reported impaired full-scale IQ, with larger effects in verbal than visual-spatial abilities. This pattern is consistent with Crow's (1990)[81] long-standing hypothesis of temporal lobe asymmetries in the etiology of schizophrenia and associated greater verbal impairment in the risk for schizophrenia.

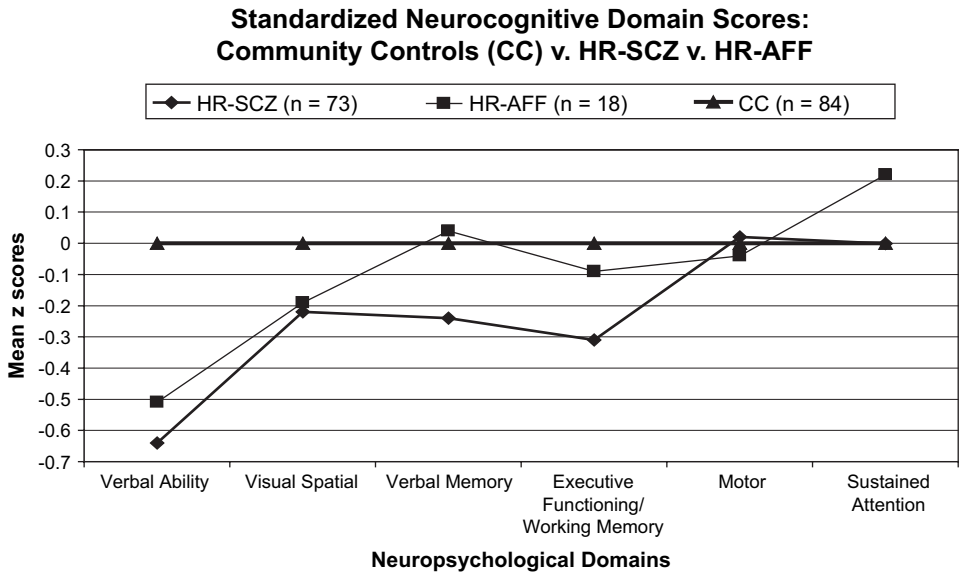

Fig. 1. Group Standardized Neurocognitive Domain Scores: Community Controls (CC) vs HR-SCZ vs HR-AFF.

The results regarding group differences in Verbal Memory were somewhat equivocal. That is, the impairment in HR-SCZ ranged from an effect size of $d = .27$ with the full group of controls to $d = .39$ with the smaller control group, which excluded participants with a family history of depression. The literature suggests an average effect size of about .5–.6 for verbal declarative memory tests in adult relatives of SCZ, which would have produced significant findings in this study. It is likely that a number of issues may have played a role in attenuating the results. These include combining different tasks and operationalizing the variable as immediate recall percentage (rather than as standard scores whose associated raw score values are not linearly distributed). In addition, an inability to make use of the delayed recall condition may have reduced sensitivity to deficit. Finally, the HAHRS and HFS studies used different types of word list-learning tasks that could not be combined. This was a limitation as the list-learning task used in HAHRS yielded significant results. Thus, we were limited in being able to use tasks that may have optimally stressed a vulnerable declarative memory system.

The small to moderate effect sizes in the Motor and Visual-Spatial domains (although the latter showed a trend in group comparisons based on the modified control group) is not unexpected as these tasks have been shown to have small to modest effect sizes in adult studies and in children at risk for psychosis (see Table 1): Pegboard tasks ($d = .18$ and .26 for dominant and nondominant hands, respectively) and Block Design ($d = .34$).[26] In general, motor abnormalities, which tend to be robust in young HR children, are not typically impaired in teenagers and young adults at genetic risk.[23]

The results for the CPT-IP were particularly surprising. No differences were found on the major performance indices for either of the 2 HR groups when compared with normal controls or with each other. In past studies, impaired sustained attention, as measured by numerous variants of the Continuous Performance Test, has been found to be one of the most robust cognitive dysfunctions associated with schizophrenia (see Cornblatt and Keilp 1994 for a review[27]). In particular, the Identical Pairs version of the CPT (CPT-IP) was very successful in identifying attentional vulnerability markers in children, adolescents, and young adults; this was especially true in first generation (1970s–1990s) of schizophrenia high-risk studies.[27,34,82–84] More recently, however, inconsistent findings have been reported, including those presented here and by Cosway et al. (2002).[85]

A number of speculative possibilities may account for the recent negative CPT-IP findings. First, and perhaps most significantly, the results reported here (and from the Edinburgh study) are cross-sectional. The CPT-IP has been most effective in predicting later behavioral difficulties, particularly emerging social impairments and adult social isolation.[34,50,86] The mix of true positives to false positives in the current sample is as yet unknown. As a result, predictive accuracy cannot be evaluated and awaits later follow-up. Another possibility includes the operation of significant cohort effects. Computerized visual attention tasks were novel when introduced in the first generation of HR studies. However, it is possible that these tasks tap a now relatively overlearned and well-developed skill set (derived from high exposure to visually based computer games that reward reaction time and accurate visual discrimination/working

Table 5. Neurocognitive Domain and Individual Test Scores Among High-Risk and Community Control (n = 72) Groups

Domain[a]/Individual Test Variable[b]	HR-SCZ (1)		HR-AFF (2)		CC (3)		Pairwise Comparisons[c]					
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	1–2	d[d]	1–3	d[d]	2–3	d[d]
Verbal Ability	73	−.79 (.79)	18	−.64 (1.3)	72	0.0 (.91)	.661	.09	**<.001**	.84	**.007**	.76
WRAT-3 Reading SS	73	99.5 (11.4)	18	101.9 (17.5)	72	108.1 (11.8)	.602	.13	**<.001**	.61	.071	.48
Vocabulary ScS	73	9.2 (2.6)	18	9.4 (3.7)	71	11.8 (3.2)	.841	.02	**<.001**	.91	**.001**	.90
Visual-Spatial	73	−.35 (.71)	18	−.32 (1.1)	72	0.0 (1.0)	.961	.02	.061	.34	.294	.36
Block Design ScS	72	9.4 (2.4)	18	9.4 (3.6)	71	10.4 (3.3)	.961	.01	.061	.35	.294	.36
Verbal Memory	73	−.36 (1.0)	18	−.08 (.98)	72	0.0 (1.0)	.321	.29	**.020**	.39	.747	.11
Story Recall Percentage	72	.47 (.13)	18	.50 (.13)	72	.51 (.13)	.321	.29	**.020**	.38	.747	.11
Executive Functioning/ Working Memory	73	−.36 (.64)	18	−.14 (.64)	72	0.0 (.73)	.207	.23	**.003**	.54	.378	.32
COWA Raw Score	73	34.2 (10.8)	18	35.2 (11.5)	72	38.0 (10.9)	.780	.09	**.020**	.43	.250	.34
Digit Span ScS	73	10.3 (2.9)	18	9.6 (2.2)	70	11.2 (3.4)	.326	.25	.140	.28	**.034**	.53
Coding/Digit Symbol ScS	72	9.2 (2.9)	18	11.5 (2.9)	70	10.2 (3.0)	**.004**	.79	**.048**	.34	.104	.44
TMT-B (sec)	73	65.9 (25.0)	18	60.3 (31.7)	71	54.5 (30.1)	.558	.14	.137	.27	.648	.13
Motor	73	−.07 (.88)	18	−.11 (1.2)	72	0.0 (.71)	.967	.08	.790	.03	.523	.11
Grooved Pegboard R (sec)	69	71.7 (17.7)	18	73.2 (17.9)	67	69.9 (13.6)	.847	.13	.718	.09	.333	.22
Grooved Pegboard L (sec)	69	78.3 (19.1)	18	75.2 (19.4)	67	77.4 (15.2)	.556	.15	.748	.05	.572	.20
TMT-A (sec)	73	27.2 (8.5)	18	27.5 (12.9)	71	25.9 (11.4)	.568	.08	.715	0.0	.733	.08
Sustained Attention	73	−.06 (.78)	18	.17 (.82)	72	0.0 (.92)	.296	.30	.443	.17	.720	.13
CPT-IP Digits d'	66	1.6 (.92)	18	1.8 (.76)	65	1.6 (.97)	.473	.20	.640	.11	.677	.09
CPT-IP Shapes d'	66	1.7 (.83)	18	1.9 (.90)	67	1.8 (.95)	.271	.33	.346	.18	.742	.15

Note: HR-SCZ = genetic high-risk for schizophrenia; HR-AFF = genetic high-risk for affective psychosis; CC = community controls.
[a]Neurocognitive domain scores are z-scores.
[b]Individual test scores reflect the actual number of subjects prior to the imputation of missing data. WRAT-3 score is a standard score (SS); subtests of the WISC-III/WAIS-R/WAIS-III (Vocabulary, Block Design, Coding/Digit Symbol) are (age-corrected) scaled scores (ScS); Story Recall Percentage is the percentage of units recalled on immediate recall condition for CMS Stories/WMS-R and WMS-III Logical Memory I; COWA (Controlled Oral Word Association test) is a raw score (total words generated); Grooved Pegboard and TMT raw scores are in seconds; CPT-IP values are d'.
[c]1–2 = HR-SCZ vs HR-AFF; 1–3 = HR-SCZ vs CC; 2–3 = HR-AFF vs CC, controlling for subject age, mean parental education, and correlated data in a mixed model; statistically significant comparisons ($p < .05$) are in boldface.
[d]d = Cohen's d based on least squared means, controlling for subject age and mean parental education.

memory), thus obscuring subtle deficits; this may be especially true of adolescents and young adults in the current generation. In addition, there is a substantial difference in the way IQ is managed in the most recent wave of HR studies. From a neurocognitive perspective, first-generation HR studies employed the perspective that a normal control group matched for the low IQ that characterizes many HR individuals was not representative of the general population, and this matching was therefore problematic in its own right. In the newer generation HR studies perspectives have changed, and it is now considered important to match on IQ or some measure of potential ability. Since attention is one of the building blocks of IQ, by controlling for IQ, attention may be highly affected and group differences minimized. Although we did not match for IQ per se, our matching for parental education is a reasonable proxy for this strategy.

Neuropsychological Functioning in HR-AFF

Results with persons at HR-AFF suggest that neurocognitive impairments may be part of the vulnerability to affective psychoses and that further research is required to clarify this association. While only the Verbal Ability function was significantly impaired, the pattern was quite similar to that observed in HR-SCZ, but to a lesser degree. Regarding the Digit Span task, on which the HR-AFF group differed significantly from the modified control group, the HR-AFF had a slightly lower performance than HR-SCZ. This is interesting because earlier findings from the New York HR study showed greater attention deficits in those at HR-SCZ than HR-AFF. While the HR-AFF sample size is too small to draw firm conclusions, if these results hold up with larger samples or in other samples, one may look to changes in diagnostic practices as a possible explanation. One probable difference between current and earlier generation HR studies is that diagnostic criteria and practices used to distinguish schizophrenia from affective psychoses changed significantly with the inception of the DSM-III in 1980. Most first-generation HR studies (reviewed in Table 1 of Niemi et al.[30]) began selection of HR subjects prior to 1980. It is possible that probands formerly considered to have schizophrenia have a higher likelihood of an affective psychosis diagnosis today.

Strengths and Limitations of the Study

This study has a number of strengths, including a relatively large sample size of people at HR for schizophrenia and community controls, and a relatively extensive neuropsychological battery covering a range of functions. Moreover, our combined control group ascertainment was not "asymmetric" with respect to our HR ascertainment, an issue addressed in some detail by Snitz et al.[26] That is, controls at both sites were selected for participation by differing from HR subjects only on 1 exclusion criterion: controls could not have a family history of psychosis in first- or second-degree relatives. There were no additional exclusion criteria that were typically imposed in past studies, such as ruling out controls with Axis I disorders, a criterion that tends to yield a "super-normal" control group. The latter ascertainment method is likely to (1) exaggerate group differences and inflate associated effect sizes and (2) leave the scientific community unable to interpret the findings as related specifically to HR status rather than the nonspecific psychopathology that is typically greater in HR relatives. In the HAHRS the control group consisted of offspring of parents, one-third of whom had an Axis I diagnosis, mainly a history of major depression. In the HFS a number of controls had nonpsychotic psychiatric diagnoses. Thus, the studies' subject selection strategy supports increased confidence that any differences are more likely due to HR status and not nonspecific psychopathology. On the other hand, some might argue that our rate of major depression in the parents was higher than expected in the general population and that our original control group, in essence, contained cases too similar to the affected groups. We addressed these issues by carrying out analyses with both broad and narrower control samples, which yielded somewhat different and informative outcomes. These results underscore the importance of control selection criteria and add to the general conclusion that genetic risk for affective disorder, including nonpsychotic types, has a negative effect on neurocognitive function. This provides further support for the importance of studying this group.

The actual performance of the controls on the measures reported in this article was generally in the average range, also arguing against a super-normal control group. Moreover, our results are quite comparable in many respects to those derived from the Edinburgh HR study, a project that is part of the more recent generation of HR projects. Most notable are the comparable verbal deficit and absence of impairment on the CPT-IP in the 2 studies.

Another strength of this study was the inclusion of an HR-AFF comparison group. While the small sample size likely reduced power to detect statistically significant between-group differences at $p < .05$, Figure 1, which shows standardized scores, supports the notion that the HR-AFF group was only slightly less impaired than HR-SCZ. Moreover, the MANCOVA directly comparing HR-SCZ and HR-AFF was clearly nonsignificant. These pilot results support the importance of further study of neuropsychological vulnerabilities in risk for affective psychosis. A limitation was the relatively small sample and the combination of HR-AFF subjects from bipolar and unipolar psychotic probands. Larger samples of homogeneous subgroups would be more informative by helping to address more clearly the specificity question in neurocognitive research. A small but growing literature suggests that HR-SCZ may be more impaired, but that there are also some verbal deficits in HR-AFF.[51]

It is reasonable to speculate that the overlapping impairments in persons at HR-SCZ and HR-AFF may stem from overlapping susceptibility genes. For example, schizophrenia and bipolar disorder are both highly heritable disorders, with genetic factors accounting for approximately 60–90% of the risk for each illness.[87] Moreover, recent research by our groups and others strongly suggests that these disorders do not separate clearly along the DSM-IV categorical boundaries. Schizophrenia and bipolar disorder patients have been found to share 65% of RNA, protein, and neurochemical abnormalities in postmortem brains from the Stanley Neuropathology Consortium.[88] From twin studies it has also been shown that each disorder shares some portion of genetic variance in common with the other.[89] Recent results from genetic linkage and association studies suggest even greater overlap in potential etiologic factors for schizophrenia and bipolar disorder than has been previously suspected, including regions of shared genetic linkage on chromosomes 13q and 22q 90 and allelic associations with several genes including Dysbindin, DAOA(G72), DISC1, BDNF and NRG1.[39,40] Craddock et al.[39] have argued that these results "suggest an overlap in genetic susceptibility across the traditional classification systems that dichotomised psychotic disorders into schizophrenia or bipolar disorder."(p200) The results of this preliminary study must also be interpreted in light of some methodological limitations. First, the absence of follow-up data limits our ability to deal with heterogeneity of outcomes and limits our ability to understand the heterogeneity of neurocognitive functioning within the HR samples. Second, while combining study samples has the advantage of increased statistical power and generalizability, it also limited the scope of neurocognitive variables that could be examined. A little more than half of each study's neurocognitive measures were not included in these analyses, potentially attenuating this study's sensitivity to neurocognitive deficits in its combined genetic HR sample. Some important tests (eg, verbal list-learning tasks) had to be left out because they were not comparable across sites. Moreover, the subtle differences in test administration may have created more error variance, thus attenuating the results. Given that differences in verbal ability represent a key finding,

this study is limited by its inability to determine if all subjects are native English speakers or learned English as a second language in childhood. Lastly, as noted previously, the analyses involving HR-AFF were regarded as preliminary given the relatively modest sample size of this group and associated limited power. Given the disparate between-group sample sizes, comparisons between the HR-SCZ and HR-AFF groups would roughly require a high-moderate effect size (of about 0.67) to be detected with an alpha of 0.5 and beta of 0.8.

Conclusions

Despite these considerations, we found that adolescents and young adults at HR-SCZ have a very similar set of neuropsychological dysfunctions to those previously described in adult first-degree relatives, and that the findings are largely consistent with recent HR studies (Edinburgh) and with our literature review. The presence of roughly similar but somewhat milder verbal deficits in persons at HR-AFF is consistent with an emerging body of literature documenting overlapping susceptibility genes in schizophrenia and bipolar psychosis. Further research focusing on HR-AFF and comparison with HR-SCZ is necessary to determine specificity. These data need to be incorporated into early identification and intervention strategies regarding the prevention and early treatment of people at risk for psychosis.

Acknowledgments

Grant support for this study was provided by MH 43518 and MH 65562 (Tsuang, Seidman); MH 46318 (Tsuang); MH 63951 (Seidman); National Association for Research on Schizophrenia and Depression (Seidman, Tsuang); Mental Illness and Neuroscience Discovery (MIND) Institute (Seidman); Massachusetts Department of Mental Health Commonwealth Research Center (Seidman); and MH 50203 (Cornblatt). We thank the following people for help in carrying out this study: Andrea Auther, Mimi Braude, Joanne Donatelli, Lisa Gabel, Jennifer Koch, Mark Korcykowski, Nikos Makris, Danielle McLaughlin, Elon Mesholam, Ruth Olsen, Caroline Patterson, Nicole Peace, Heidi Wencel-Thermenos, Rosemary Toomey, Lynda Tucker, Sharon White, and Kristen Woodbery. We also thank Robert Heinssen for supporting this collaborative effort through the National Institute of Mental Health North American Prodromal Longitudinal Studies network. Dr. Seidman presented some of the neuropsychological data from the Harvard Adolescent High Risk Study at the annual meeting of the American Academy of Child and Adolescent Psychiatry, Miami, FL, October 2003 (''Neuropsychological functioning in adolescent offspring and siblings of persons with schizophrenia'') and at the fourth international conference on Early Psychosis, Vancouver, Canada, September 30, 2004 (''Neurocognitive and functional MRI abnormalities in adolescents at genetic risk for schizophrenia'').

References

1. Tsuang M, Stone W, Faraone S. Schizophrenia: a review of genetic studies. *Harv Rev Psychiatry.* 1999;7:185–207.
2. Gottesman I, Gould T. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry.* 2003;160:636–645.
3. Tsuang M, Gilbertson M, Faraone S. Genetic transmission of negative and positive symptoms in the biological relatives of schizophrenics. In: Marneros A, Andersen N, Tsuang M, eds. *Negative Versus Positive Schizophrenia.* Berlin: Springer; 1991:265–291.
4. Green M. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry.* 1996; 153:321–330.
5. Nuechterlein K, Dawson M. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophr Bull.* 1984;10:160–203.
6. Seidman L. Schizophrenia and brain dysfunction: an integration of recent neurodiagnostic findings. *Psychol Bull.* 1983;94:195–238.
7. Heinrichs R, Zakzanis K. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology.* 1998;12:426–445.
8. Kraepelin E. *Dementia Praecox and Paraphrenia.* Edinburgh: E & S Livingstone; 1919.
9. Bleuler E. *Dementia Praecox or the Group of Schizophrenias.* New York, NY: International Universities Press; 1911.
10. Green M, Kern R, Braff D, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the ''right stuff''? *Schizophr Bull.* 2000;26:119–136.
11. Mishara A, Goldberg T. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biol Psychiatry.* 2004;55:1013–1022.
12. Keefe R, Perkins D, Silva S, Lieberman J. The effect of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull.* 1999;25:201–222.
13. Harvey P, Keefe R. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry.* 2001;158:176–184.
14. Murray R, Lewis S. Is schizophrenia a neurodevelopmental disorder? *BMJ (Clin Research Ed).* 1987;295:681–682.
15. Weinberger D. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry.* 1987;44:660–669.
16. Woods B. Is schizophrenia a progressive neurodevelopmental disorder? toward a unitary pathogenic mechanism. *Am J Psychiatry.* 1998;155:1661–1670.
17. Cornblatt B, Lencz T, Correll C, Smith C, Auther A. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophr Bull.* 2003;29:633–651.
18. McGlashan T, Miller T, Woods S, Hoffman R, Davidson L. A scale for the assessment of prodromal symptoms and states. In: Miller T, Mednick S, McGlashan T, Liberger J, Johannessen J, eds. *Early Intervention in Psychotic Disorders.* Dordrecht, The Netherlands: Kluwer Academic Publishers; 2001:135–149.

19. McGorry P, Yung A, Phillips L. The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophr Bull.* 2003;29:771–790.
20. Gottesman I. *Schizophrenia Genesis: The Origin of Madness.* New York, NY: Freeman; 1991.
21. Faraone S, Green A, Seidman L, Tsuang M. "Schizotaxia": clinical implications and new directions for research. *Schizophr Bull.* 2001;27:1–18.
22. Kremen W, Hoff A. Neurocognitive deficits in biological relatives of individuals with schizophrenia. In: Stone W, Faraone S, Tsuang M, eds. *Early Clinical Intervention and Prevention in Schizophrenia.* Totowa, NJ: Humana Press; 2004:133–154.
23. Kremen W, Seidman L, Pepple J, Lyons M, Tsuang M, Faraone S. Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophr Bull.* 1994;20: 96–108.
24. Seidman L. Clinical neuroscience and epidemiology in schizophrenia. *Harv Rev Psychiatry.* 1997;3:338–342.
25. Sitskoorn M, Aleman A, Ebisch S, Appels M, Kahn R. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr Res.* 2004;71:285–295.
26. Snitz B, McDonald A, Carter C. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull.* 2006;32:179–194.
27. Cornblatt B, Keilp J. Impaired attention, genetics, and the pathophysiology of schizophrenia. *Schizophr Bull.* 1994;20:31–46.
28. Faraone S, Seidman L, Kremen W, Toomey R, Pepple J, Tsuang M. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a four-year follow-up study. *J Abnorm Psychol.* 1999;108:176–181.
29. Faraone S, Seidman L, Kremen W, Toomey R, Pepple J, Tsuang M. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. *Biol Psychiatry.* 2000;48:120–126.
30. Niemi L, Suvisaari J, Tuulio-Henriksson A, Lonnqvist J. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophr Res.* 2003;60: 239–258.
31. Keshavan M, Diwadkar V, Montrose D, Rajarethinam R, Sweeney J. Premorbid indicators and risk for schizophrenia: a selective review and update. *Schizophr Res.* 2005;79:45–57.
32. Seidman L, Thermenos H, Poldrack R, et al. Altered brain activation in dorsolateral prefrontal cortex in adolescents and young adults at genetic risk for schizophrenia: an fMRI study of working memory. *Schizophr Res.* In press.
33. Stone W, Faraone S, Seidman L, Olson E, Tsuang M. Searching for the liability to schizophrenia: concepts and methods underlying genetic high-risk studies of adolescents. *J Child Adolesc Psychopharmacol.* 2005;15:403–417.
34. Cornblatt B, Obuchowski M, Schnur D, O'Brien J. Hillside study of risk and early detection in schizophrenia. *Br J Psychiatry Suppl.* 1998;172:26–32.
35. Davalos D, Compagnon N, Heinlein S, Ross R. Neuropsychological deficits in children associated with increased familiar risk for schizophrenia. *Schizophr Res.* 2004;67:123–130.
36. Cornblatt B, Winters L, Erlenmeyer-Kimling L. Attentional markers of schizophrenia: evidence from the New York High-Risk Study. In: Schulz S, Tamminga C, eds. *Schizophrenia: Scientific Progress.* New York, NY: Oxford University Press; 1989:83–92.
37. Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK. Toward constructing an endophenotype strategy for bipolar disorders. *Biol Psychiatry.* In press.
38. Berrettini W. Susceptibility loci for bipolar disorder: overlap with inherited vulnerability to schizophrenia. *Biol Psychiatry.* 2000;47:245–251.
39. Craddock N, O'Donovan M, Owen M. Genes for schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet.* 2005;42:193–204.
40. Craddock N, O'Donovan M, Owen M. The genetics of schizophrenia and bipolar disorder: implications for psychiatric nosology. *Schizophr Bull.* 2006;32:9–16.
41. Seidman L, Kremen W, Koren D, Faraone S, Goldstein J, Tsuang M. A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. *Schizophr Res.* 2002;53:31–44.
42. Park S, Holzman P. Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry.* 1992;49:975–982.
43. Pirkola T, Tuulio-Henriksson A, Glahn D, et al. Spatial working memory function in twins with schizophrenia and bipolar disorder. *Biol Psychiatry.* 2005;25:930–936.
44. Gourovitch M, Torrey E, Gold J, Randolph C, Weinberger D, Goldberg T. Neuropsychological performance of monozygotic twins discordant for bipolar disorder. *Biol Psychiatry.* 1999;45:639–646.
45. Kieseppa T, Tuulio-Henriksson A, Haukka J, et al. Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information-processing speed. *Psychol Med.* 2005;35:205–215.
46. Keri S, Kelemen O, Benedek G, Janka Z. Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. *Psychol Med.* 2001;31:915–922.
47. Kremen W, Faraone S, Seidman L, Pepple J, Tsuang M. Neuropsychological risk indicators for schizophrenia: a preliminary study of female relatives of schizophrenic and bipolar patients. *Psychiatr Res.* 1998;79:227–240.
48. Ferrier I, Chowdhury R, Thompson J, Watson S, Young A. Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. *Bipolar Disord.* 2004;6:319–322.
49. Goldstein J, Seidman L, Buka S, et al. Impact of genetic vulnerability and chronic exposure to hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychosis. *Schizophr Bull.* 2000;26: 323–334.
50. Cornblatt B, Erlenmeyer-Kimling L. Global attentional deviance as a marker of risk for schizophrenia: specificity and predictive validity. *J Abnorm Psychol.* 1985;94: 470–486.
51. Schubert E, McNeil T. Neuropsychological impairment and its neurological correlates in adult offspring with heightened risk for schizophrenia and affective psychosis. *Am J Psychiatry.* 2005;162:758–766.
52. Benes F. A neurodevelopmental approach to understanding schizophrenia and other mental disorders. In: Cicchetti D, Cohen D, eds. *Developmental Psychopathology: Theory and Methods.* New York, NY: Wiley; 1995:227–253.
53. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res.* 1982;17:319–334.
54. Keshavan M. Development, disease, and degeneration in schizophrenia: a unitary pathophysiological model. *J Psychiatr Res.* 1999;33:513–522.

55. Cornblatt B, Obuchowski M. Update of high-risk research: 1987–1997. *Int Rev Psychiatry.* 1997;9:437–447.
56. Stone W, Faraone S, Tsuang M. *Early Clinical Intervention and Prevention of Schizophrenia.* Totowa, NJ: Humana Press; 2004.
57. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).* Washington, DC: American Psychiatric Association; 1994.
58. Nurnberger JJ, Blehar M, Kaufman C, et al. Diagnostic interview for genetic studies: rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry.* 1994;51:849–859.
59. Maxwell M. *Family Instrument for Genetic Studies (FIGS)* Washington, DC: Clinical Neurogenetics Branch, Intramural Research Program, National Institute of Mental Health; 1996.
60. Geller B, Zimmerman B, Williams M, Frazier J. *WASH-U-KSADS: Washington University at St. Louis Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia—Lifetime and Present Episode Version for DSM-IV.* St. Louis, Mo: Washington University School of Medicine; 1994.
61. Orvaschel H, Puig-Antich P. *The Kiddie-SADS-E (5th Revision).* Ft Lauderdale, Fla: Center for Psychological Studies, Nova Southeastern University; 1994.
62. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children—Third Edition.* San Antonio, Tex: Psychological Corporation; 1991.
63. Wechsler D. *Wechsler Adult Intelligence Scale—Third Edition.* San Antonio, Tex: Psychological Corporation; 1997.
64. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale—Revised.* San Antonio, Tex: Psychological Corporation; 1981.
65. Wilkinson G. *Wide Range Achievement Test, Administration Manual.* 3d ed. Wilmington, Del: Wide Range Inc; 1993.
66. Cornblatt B, Risch N, Faris G, Friedman D, Erlenmeyer-Kimling L. The Continuous Performance Test, Identical Pairs version (CPT-IP): I. new findings about sustained attention in normal families. *Psychiatr Res.* 1988;26: 223–238.
67. Reitan R, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* 2d ed. Tucson, Ariz: Neuropsychology Press; 1993.
68. Wechsler D. *Manual for the Wechsler Memory Scale—Third Edition.* San Antonio, Tex: Psychological Corporation; 1997.
69. Cohen M. *Children's Memory Scale.* San Antonio, Tex: Psychological Corporation; 1997.
70. Wechsler D. *The Wechsler Memory Scale—Revised: Manual.* San Antonio, Tex: Psychological Corporation; 1987.
71. Spreen O, Benton A. *Neurosensory Center Comprehensive Examination for Aphasia (NCCEA).* Victoria: University of Victoria Neuropsychology Laboratory; 1977.
72. Benton A, Hamsher K, Sivan A. *Multilingual Aphasia Examination.* 3d ed. Iowa City, Iowa: AJA Associates; 1983.
73. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary.* New York, NY: Oxford University Press; 1998.
74. Faraone S, Seidman L, Kremen W, Pepple J, Lyons M, Tsuang M. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. *J Abnorm Psychol.* 1995;104:286–304.
75. Huber P. The behavior of maximum likelihood estimates under non-standard conditions. *In: Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability* vol 1. Berkeley: University of California Press; 1967: 221–233.
76. Cosway R, Byrne M, Clafferty R, et al. Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychol Med.* 2000;30:1111–1121.
77. Byrne M, Hodges A, Grant E, Owens D, Johnstone E. Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS). *Psychol Med.* 1999;29:1161–1173.
78. Byrne M, Clafferty R, Cosway R, et al. Neuropsychology, genetic liability and psychotic symptoms in those at high risk for schizophrenia. *J Abnorm Psychol.* 2003;112:38–48.
79. Niendam T, Bearden C, Rosso I, et al. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am J Psychiatry.* 2003;160: 2060–2062.
80. Goldberg T, Aloia M, Gourovitch M, et al. Cognitive substrates of thought disorder: I. the semantic system. *Am J Psychiatry.* 1998;155:1671–1676.
81. Crow T. Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophr Bull.* 1990;16:433–443.
82. Cornblatt B, Obuchowski M, Roberts S, Pollack S, Erlenmeyer-Kimling L. Cognitive and behavioral precursors of schizophrenia. *Dev Psychopathol.* 1999;11:487–508.
83. Franke P, Maier W, Hain C, Cornblatt B. Attentional abilities and measures of schizotypy: their variation and covariation in schizophrenic patients, their siblings, and normal control subjects. *Psychiatr Res.* 1994;54:259–272.
84. Laurent A, Saoud M, Bougeral T, et al. Attentional deficits in patients with schizophrenia and in their non-psychotic first-degree relatives. *Psychiatr Res.* 1999;89:147–159.
85. Cosway R, Byrne M, Clafferty R, et al. Sustained attention in young people at high risk for schizophrenia. *Psychol Med.* 2002;32:277–286.
86. Cornblatt B, Lenzenweger M, Dworkin R, Erlenmeyer-Kimling L. Childhood attentional dysfunctions predict social deficits in unaffected adults at risk for schizophrenia. *Br J Psychiatry Suppl.* 1992;18:59–64.
87. Cardno A, Marshall E, Coid B, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch Gen Psychiatry.* 1999;56:162–168.
88. Torrey E, Barci B, Webster M, Bartko J, Meador-Woodruff J, Knable M. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biol Psychiatry.* 2005;57:252–260.
89. Cardno A, Rijsdijk F, Sham P, Murray R, McGuffin P. A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry.* 2002;59:539–545.
90. Badner J, Gershon E. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol Psychiatry.* 2002;7:405–411.
91. Mednick SA, Schulsinger F. Some premorbid characteristics relating to breakdown in children with schizophrenic mothers. In: Rosenthal D, Kety SS, eds. *The Transmission of Schizophrenia.* Oxford, UK: Pergamon Press; 1968: 267–291.
92. Landau R, Harth P, Othnay N, Scharfhertz C. The influence of psychotic parents on their children's development. *Am J Psychiatry.* 1972;129:70–75.

93. Asarnow JR, Steffy RA, MacCrimmon DJ, Cleghorn JM. An attentional assessment of foster children at risk for schizophrenia. In: Wynne LC, Cromwell RL, Matthysse S, eds. *The Nature of Schizophrenia: New Approaches to Research and Treatment.* New York, NY: John Wiley; 1978:339–358.
94. Schreiber H, Stolz-Born G, Heinrich H, Kornhuber HH, Born J. Attention, cognition, and motor perseveration in adolescents at genetic risk for schizophrenia and control subjects. *Psychiatr Res.* 1992;44:125–140.
95. Maier W, Franke P, Kopp B, Hardt J, Hain CH, Rist F. Reaction time paradigms in subjects at risk for schizophrenia. *Schizophr Res.* 1994;13:35–43.
96. Lifshitz M, Kugelmass S, Karov M. Perceptual-motor and memory performance of high-risk children. *Schizophr Bull.* 1985;11:74–84.
97. Winters KC, Stone AA, Weintraub S, Neale JM. Cognitive and attentional deficits in children vulnerable to psychopathology. *J Abnorm Child Psychol.* 1981;9:435–453.
98. Sohlberg SC. Personality and neuropsychological performance of high-risk children. *Schizophr Bull.* 1985;11:48–60.
99. Erlenmeyer-Kimling L, Cornblatt BA. Attentional measures in a study of children at high risk for schizophrenia. In: Wynne LC, Cromwell RL, Matthysse S, eds. *The Nature of Schizophrenia: New Approaches to Research and Treatment.* New York NY: John Wiley; 1978:359–365.
100. Rutschmann J, Cornblatt BA, Erlenmeyer-Kimling L. Auditory recognition memory in adolescents at risk for schizophrenia: report on a verbal continuous recognition task. *Psychiatr Res.* 1980;3:151–161.
101. Harvey P, Winters K, Weintraub S, Neale JM. Distractibility in children vulnerable to psychopathology. *J Abnorm Psychol.* 1981;90:298–304.
102. Orvaschel H, Mednick S, Schulsinger F, Rock D. The children of psychiatrically disturbed parents: differences as a function of the sex of the sick parents. *Arch Gen Psychiatry.* 1979;36:691–695.
103. Hallet S, Quinn D, Hewitt J. Defective interhemispheric integration and anomalous language lateralization in children at risk for schizophrenia. *J Nerv Ment Dis.* 1986;174:418–427.
104. Cornblatt B, Erlenmeyer-Kimling L. Early attentional predictors of adolescent's behavioral disturbances in children at risk for schizophrenia. In: Watt NF, Anthony EJ, Wynne LC, Rolf JE, eds. *Children at Risk for Schizophrenia: A Longitudinal Perspective.* New York, NY: Cambridge University Press; 1984:198–211.
105. Driscoll RM. Intentional and incidental learning in children vulnerable to psychopathology. In: Watt NF, Anthony EJ, Wynne LC, Rolf JE, eds. *Children at Risk for Schizophrenia: A Longitudinal Perspective.* New York, NY: Cambridge University Press; 1984:320–325.
106. Grunebaum H, Weiss JL, Gallant D, Cohler BJ. Attention in young children of psychotic mothers. *Am J Psychiatry.* 1974;131:887–891.
107. Asarnow JR, Steffy RA, MacCrimmon DJ, Cleghorn JM. An attentional assessment of foster children at risk for schizophrenia. *J Abnorm Psychol.* 1977;86:267–275.
108. Cohler BJ, Grunebaum HU, Weiss JL, Gamer E, Gallant DH. Disturbance of attention among schizophrenic, depressed and well mothers and their young children. *J Child Psychol Psychiatry.* 1977;18:115–135.
109. Rutschmann J, Cornblatt B, Erlenmeyer-Kimling L. Sustained attention in children at risk for schizophrenia: findings with two visual continuous performance tests in a new sample. *J Abnorm Child Psychol.* 1986;14:365–385.
110. Nuechterlein KH. Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *J Abnorm Psychol.* 1983;92:4–28.
111. Rutschmann J, Cornblatt BA, Erlenmeyer-Kimling L. Sustained attention in children at risk for schizophrenia. *Arch Gen Psychiatry.* 1977;34:571–575.
112. Erlenmeyer-Kimling L, Cornblatt BA. Summary of attentional findings in the New York High-Risk Project. *J Psychiatr Res.* 1992;26:405–426.
113. Erlenmeyer-Kimling L, Cornblatt B, Friedman D, et al. Neurological, electrophysiological, and attentional deviations in children at risk for schizophrenia. In: Henn FA, Nasrallah HA, eds. *Schizophrenia as a Brain Disease.* New York, NY: Oxford University Press; 1982:61–98.
114. Neale JM, Winters KC, Weintraub S. Information-processing deficits in children at high risk for schizophrenia. In: Watt NF, Anthony EJ, Wynne LC, Rolf JE, eds. *Children at Risk for Schizophrenia: A Longitudinal Perspective.* New York, NY: Cambridge University Press; 1984:264–277.
115. Wolf LE, Cornblatt BA, Roberts SA, Shapiro BM, Erlenmeyer-Kimling L. Wisconsin Card Sorting deficits in the offspring of schizophrenics in the New York High Risk Project. *Schizophr Res.* 2002;57:173–182.
116. Hallet S, Green P. Possible defects of interhemispheric integration of children of schizophrenics. *J Nerv Ment Dis.* 1983;171:421–425.
117. Rieder R, Broman S, Rosenthal D. The offspring of schizophrenics: II. perinatal factors and IQ. *Arch Gen Psychiatry.* 1977;34:789–799.
118. Goodman SH. Emory University project on children of disturbed parents. *Schizophr Bull.* 1987;13:411–423.
119. Dworkin RH, Cornblatt BA, Friedmann R, et al. Childhood precursors of affective vs. social deficits in adolescents at risk for schizophrenia. *Schizophr Bull.* 1993;19:563–577.
120. Cannon T, Bearden C, Hollister J, Rosso I, Sanchez L, Hadley T. Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull.* 2000;2000:379–393.
121. Klein RH, Salzman LF. Response-contingent learning in children at risk. In: Watt NF, Anthony EJ, Wynne LC, Rolf JE, eds. *Children at Risk for Schizophrenia: A Longitudinal Perspective.* New York, NY: Cambridge University Press; 1972:371–375.
122. Worland J, Weeks D, Janes C, Strock B. Intelligence, classroom behavior, and academic achievement in children at high and low risk for psychopathology: a structural equation analysis. *J Abnorm Child Psychol.* 1984;12:437–454.
123. Sameroff A, Barocas R, Seifer R. The early development of children born to mentally ill women. In: Watt NF, Anthony EJ, Wynne LC, Rolf JE, eds. *Children at Risk for Schizophrenia: A Longitudinal Perspective.* New York, NY: Cambridge University Press; 1984:482–513.
124. Sohlberg S, Yaniv S. Social adjustment and cognitive performance of high-risk children. *Schizophr Bull.* 1985;11:61–65.